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Gender and sex independently associate with common somatic symptoms and lifetime prevalence of chronic disease

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ABSTRACT

Sex and gender influence health differently. Associations between sex and health have been extensively studied, but gender (i.e. psychosocial sex) has been largely neglected, partly due to the absence of gender measures in cohort studies. Therefore, our objective was to test the unique associations of gender and sex with common somatic symptoms and chronic diseases, using a gender index created from existing cohort data. We applied LASSO logistic regression to identify, out of 153 unique variables, psychosocial variables that were predictive of sex (i.e. gender-related) in the Dutch LifeLines Cohort Study. These psychosocial variables covered gender roles and institutionalized gender. Using the estimated coefficients, gender indexes were calculated for each adult participant in the study (n = 152,728; 58.5% female; mean age 44.6 (13.1) years). We applied multiple ordinal and logistic regression to test the unique associations of the gender index and sex, and their interactions, with common somatic symptoms assessed by the SCL-90 SOM and self-reported lifetime prevalence of chronic diseases, respectively. We found that in 10.1% of the participants the gender index was not in line with participants' sex: 12.5% of men and 8.4% of women showed a discrepancy between gender index and sex. Feminine gender characteristics are associated with increased common somatic symptoms and chronic diseases, especially in men. Female sex is associated with a higher common somatic symptom burden, but not with a higher prevalence of chronic diseases. The study shows that gender and sex uniquely impact health, and should be considered in epidemiological studies. Our methodology shows that consideration of gender measures in studies is necessary and feasible, based on data generally present in cohort studies.

Sex and gender are increasingly recognized as essential aspects within health research (Pardue and Wizemann, 2001; Phillips, 2011; Springer et al., 2012). Sex differences in the distribution and presentation of common somatic symptoms and medical conditions have been found, including in cardiovascular disease and depression, as well as in responses to treatments of these (Labaka et al., 2018; Spence and Pilote, 2015; Tomenson et al., 2013). However, gender differences remain largely neglected in health research (Nowatzki and Grant, 2011). This is problematic, as evidence suggests that studying the roles of both sex and gender may reveal additional insights into their respective contribution in disease development, help-seeking behavior and response to treatment (Nowatzki and Grant, 2011; Phillips, 2011; Smith and Koehoorn, 2013).

To understand the importance of incorporating gender into health research, one should clearly distinguish between the concepts of sex and gender. Biological sex is defined as one's biological attributes, including physical features, chromosomes, gene expression, hormones and anatomy (Johnson et al., 2007). Yet, intersex variations exist in approximately 1.7% of the general population, challenging beliefs in absolute dimorphisms (Blackless et al., 2000). Gender, in contrast, can be seen as the psychosocial equivalent of biological sex: it encompasses the socially constructed roles, behaviors, identities and relationships of women, men and gender-diverse people in a given time and society (Smith and Koehoorn, 2013). In short, gender has a broader scope than sex and often refers to socially prescribed roles and behaviors, and experienced dimensions that relate to femininity and masculinity (Bottorff et al., 2011). In general, gender roles, and the embodiment hereof, are not as static as one's biological sex usually is. They are

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subjected to ever-changing societal norms and institutions and may impact one's opportunities in life (Johnson et al., 2007).

Examples of differing associations of sex and gender roles with health can be found in multiple common medical conditions. For example, it is known that females develop osteoporosis more frequently due to biological differences in bone density and hormone levels (Alswat, 2017). Simultaneously, gender roles may encourage females (and feminine males) to restrict their food intake and perform sports not involving heavy weightlifting, further increasing their risk of developing osteoporosis (Noh et al., 2018). Another example can be seen in healthcare seeking behavior and treatment allocation (Galdas et al., 2005). Masculine gender roles may affect help-seeking behavior and hamper adequate diagnosis and treatment, for example in depressive symptoms, as masculine gender roles are thought to be less expressive and to not openly acknowledge pain or impairments compared to feminine gender roles (Barsky et al., 2001; Lee and Owens, 2002). Disentangling associations of sex and gender with health may enhance our insights towards effective medicine in a given society.

Although the association of sex with health is often incorporated, the association of gender roles with health is seldom considered in research (Nowatzki and Grant, 2011; Tannenbaum et al., 2019). Therefore, little is known about whether sex and gender roles uniquely associate with symptoms and diagnoses. Similarly, whether these associations are present amongst a variety of health issues or merely specific symptoms, and whether associations differ between women and men, remains unknown. These gaps in knowledge may be attributable to difficulties in measuring gender. Existing gender measures, such as the Bem Sex Role Inventory (BSRI) (Bem, 1974; Hoffman and Borders, 2001), Personal Attributes Questionnaire (PAQ) (Helmreich et al., 1981) and gender diagnosticity measures (Lippa and Connelly, 1990) have been extensively criticized. These instruments measure gender via items that stereotype masculine and feminine characteristics, whilst gender roles are a broader concept largely dependent on time and place (Choi et al., 2008; Hoffman and Borders, 2001; Pedhazur; Tetenbaum, 1979). Possibly due to these difficulties, most epidemiological cohort studies do not measure gender in any way.

To the best of our knowledge, we present the first comprehensive analyses of the associations of sex and gender with health in a large epidemiological study: the general population cohort LifeLines. To this end, we constructed a gender index based on the existing data. We hypothesized that sex and the gender index will have a unique association with common somatic symptoms, as well as the lifetime prevalence of chronic disease. We also expected that female sex and feminine gender indexes will be associated with higher symptom levels and lifetime prevalence of chronic disease and that the associations of gender differ per sex.

1. Methods

1.1. Participants

This study was performed in LifeLines. Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviors of 167,729 persons living in the North of The Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. Extensive information on the cohort and recruitment is provided elsewhere (Klijs et al., 2015; Scholtens et al., 2015). The current study was based on the 152,728 adults included at baseline (Table 1). The LifeLines Cohort Study is performed according to the principles of the Declaration of Helsinki and in accordance with UMCG's research code. The LifeLines Cohort Study is approved by the Medical Ethical Committee of the University Medical Center Groningen, The Netherlands.

1.2. Collected data

At baseline, participants completed questionnaires on topics including, but not limited to demographics, health, lifestyle and psychosocial aspects. Additionally, participants underwent physical examinations and biological samples, including DNA, were collected (Scholtens et al., 2015). DNA material of 15,000 participants (9.8% of participating adults) was analyzed with 12-sample HumanCytoSNP-12 BeadChips. Quality control measures included i) exclusion of material with a call-rate < 95%, ii) duplicate material, iii) chromosome X heterozygosity was > 0.005 (for municipally-registered males) or chromosome X heterozygosity was < 0.1 (for municipally-registered females), and iv) material when sex chromosomes did not correspond with municipally-registered gender.

1.3. Subsample for calculation of the gender index

We conducted the analyses to calculate gender indexes on the subsample of participants from whom DNA was analyzed. We suspected that participants with an intersex condition or non-conform gender identity are more likely to have discrepancies between their psychosocial and biological sex, thus these were excluded from the analyses to compose the gender index (Furtado et al., 2012).

We defined intersex conditions as chromosomal variations of the sex-chromosomes (e.g. Triple-X syndrome); genetic mutation(s) resulting in hormonal disturbances relevant for sexual development (e.g. congenital adrenal hyperplasia); or extreme variations of internal and/or external genital organs (e.g. uterus didelphys or micropenis). In line with previous research, we also included more common variations of the external organs such as hypospadias, cryptorchism (for which an operation was needed), uterus anomalies or a vaginal septum as intersex conditions (Blackless et al., 2000). Although such common variations are generally not considered expressions of intersex conditions, we excluded all participants with any variations in this stereotype appearance, so that we include the most stereotypic women and men from a biological viewpoint (see Appendix A.1 for more details).

Complementing approaches were applied to identify participants with an intersex condition (Appendix A.2). Firstly, the subsample of participants who's DNA had passed the earlier described quality control (n = 13,395) was selected, since this selection excluded participants with copy number variations of the sex chromosomes, SRY-gene abnormalities, or participants with an officially changed transgender identity. Secondly, text fields asking about disorders, birth defects and operations were searched for expressions of potential intersex variations, intersex birth defects and sex-related operations, respectively. Lastly, we considered all biological males who used prescribed estrogens and all biological females who used prescribed testosterone transgender in the current study. Ultimately, 74 participants within the subsample were labeled as 'highly likely' of having an intersex condition or non-conform gender identity and were excluded (Appendix A.3). This resulted in a subsample of n = 13,321 to construct a gender index.

1.4. Gender-related variables

All psychological and social variables are included in the model to construct the gender index, as far as these meet both of the following criteria: i) the variable is not reflecting a momentary emotional state that strongly fluctuates over short time periods and ii) the variable has < 40% missing values. Since the included questionnaires were not originally constructed to identify potential psychosocial differences according to sex, potential sex-related differences are more likely to be found in single items, than in sumscores of questionnaires. Therefore, we included item-level variables. Only for the NEO-PI-R (Costa and McCrae, 1992), which assesses personality traits, we included mean subscale scores, rather than item scores, because we did not expect individual items to differ more between sexes than subscales would.

Table 1
Overview of demographic characteristics of the subsample on which the gender index is based and the complete adult Lifelines cohort at baseline.

Characteristic		Subsample Gender index (n = 13,321)	Adult Lifelines Cohort (n = 152,728)
Source into study (%)	Family	3786 (28.3%)	49,264 (32.5%)
	GP	8653 (64.4%)	81,533 (53.4%)
	Self-registered	956 (7.1%)	21,571 (14.1%)
Mean age in years (SD)		48.1 (11.4)	44.6 (13.1)
Sex (%)	Male	5598 (41.8%)	63,388 (41.5%)
	Female	7797 (58.2%)	89,340 (58.5%)
Median gender index (IQR)	Male	0.05 (0.01–0.19)	0.06 (0.01–0.24)
	Female	0.97 (0.88–0.99)	0.96 (0.83–0.99)
Intersex conditions (%)		74 (0.55%)	1309 (0.86%)
Currently smoking (%)		3113 (23.2%)	32,758 (21.4%)
Alcohol (%)	< 1 time a month	4365 (32.6%)	31,195 (20.4%)
	1 to 3 times a month	3827 (28.6%)	29,818 (19.5%)
	1 to 5 times a week	5240 (39.1%)	75,141 (49.2%)
	6 to 7 times a week	1448 (10.8%)	16,574 (10.9%)
Currently in a relationship (%)		11,663 (87.1%)	129,129 (84.5%)
Education (%)	No, primary or other education	768 (5.7%)	7380 (4.8%)
	Preparatory, vocational or junior secondary education	4381 (32.7%)	41496 (27.2%)
	Senior secondary education or higher vocational education	3885 (29.0%)	48741 (31.9%)
	University education	615 (4.6%)	9199 (6.0%)
Median SCL-90 SOM sumscore (IQR)	Male	1.17 (1.08–1.42)	1.17 (1.08–1.42)
	Female	1.33 (1.09–1.58)	1.33 (1.17–1.58)

This resulted in 153 variables, consisting of 145 single variables and 8 personality subscales, included in the analyses. These variables cover three of the four gender aspects which were previously defined, namely gender roles, gender dynamics and institutionalized gender (Johnson et al., 2007; Pelletier et al., 2015). Appendix B provides information on included variables.

1.5. Statistical analyses

1.5.1. Elastic net regularized generalized linear model

Based upon visual inspection of missing data patterns of the adult Lifelines population with the VIM Package 4.8.0, we concluded that there is no strong indication of data missing not at random and therefore multiple imputation with Mice Package 3.3.0 in R Studio 1.1.383 was performed (van Buuren and Groothuis-Oudshoorn, 2011). Age, municipally-registered sex and source of entry into the study were always included as predictor variables for the multiple imputation. In total, 73% of all participants had at least one missing value on a variable that was relevant to construct the gender index. The variable with the highest frequency of missing data (20.9% of all participants) was membership of a social club. The minimal correlation of potential predictors with the variable to be imputed was 0.1. To construct a gender index, 245 variables (derived from 153 unique psychosocial variables potentially related to sex) were entered into an elastic net regularized generalized linear model with sex as dichotomous outcome (n = 13,321) (Zou and Hastie, 2005). This method retains parsimonious number of variables, which are highly predictive for the outcome and attains a high predictive accuracy of the model (Zou and Hastie, 2005; Hastie and Qian, 2014). The data was randomly assigned to a training set (80%; n = 10,657), and a testing set (20%, n = 2664). The former set was used to estimate coefficients: larger estimated coefficients indicate greater importance in discriminating between sexes. The latter set was used to calculate the model's predictive accuracy. The optimal regularization parameter α was selected by a grid search with the same 10-fold cross-validation for three αs, namely 0.1, 0.5 and 1.0. For the predictive model with the optimal α, the value of λ that minimized the mean squared error (MSE) was selected by 10-fold cross-validation, as was λ plus one standard error: $\lambda.1se$. The area under the receiving operating characteristic-curve (AUC) was calculated when predicting classification of participants into 'male' or 'female' as the measure of goodness of fit. To provide an overview of the most discriminative gender-related variables, a model with the AUC of 0.80, generally already interpreted as 'good' classifying accuracy, was calculated as well in the test set.

Estimates of the coefficients obtained through the aforementioned regression ultimately formed the basis of the composite gender index that was applied to each adult Lifeline participant (n = 152,728). The gender index is a continuum, ranging from 0% to 100%, representing the probability of each individual being a woman: the higher the gender index, the more feminine characteristics a person has. Androgyny is indicated by an index of 50%, where equal levels of feminine and masculine characteristics are present.

1.5.2. Analyses of common somatic symptoms and chronic diseases

Previous studies showed that age and educational levels are associated with gender roles (Koenig, 2018; Miller and Chamberlin, 2000), thus we performed two-way ANOVAs to assess whether the magnitude of difference in gender index between sexes was equal across age groups (18–44, 45–64, 65+) (Hilderink et al., 2013) and educational levels (low, medium, high) (van Zon et al., 2017) in the current study.

Twelve multiple ordinal regressions were conducted to investigate whether sex and the gender index independently have an association with common somatic symptoms in the general population. Assumptions of ordinal regression were met (O'Connell, 2006). Common somatic symptoms were assessed with the 12-item ordinal Symptom CheckList-90 Somatization subscale (SCL-90 SOM), which has been recommended for large scale studies (Zijlema et al., 2013). The 12 items had five Likert-response options. We used multiple linear regression to investigate the associations of the gender index and sex with the SCL-90 SOM sumscore.

To test the associations of sex and the gender index with the lifetime prevalence of chronic diseases, we performed twelve multiple logistic regression analyses. Diseases that were identified by the Dutch Ministry of Health, Welfare and Sport as causing the greatest loss of healthy life years per person in the Netherlands were identified amongst Lifelines participants (Dutch Ministry of Health, Welfare and Sports, 2019; Gijsen et al., 2013; Hoeymans et al., 2013). At baseline, self-reported lifetime prevalence hereof was measured. Low-prevalent (e.g. dementia) and sex-specific diseases (e.g. pregnancy diabetes) were excluded from the analyses (Green, 1991). Validity of the logistic regression's linearity assumption was violated for cardiovascular diseases (CVD; encompassing arrhythmia, heart failures and heart attack), skin cancer, epilepsy and asthma/COPD. Thus, gender indexes were categorized into quartiles that were included in the respective models. As a

sensitivity analysis, categorization of gender indexes by means of a split at the median yielded comparable results.

We tested interaction terms between the gender index and sex for significance. We assessed multicollinearity of the variables by the variance inflation factor (VIF). No problems with multicollinearity were found, as VIF was < 5 in all analyses. For all the above-mentioned analyses, we provided analysis codes in OSF (https://osf.io/z9aw4/) to increase transparency of the study.

2. Results

2.1. The gender index

The gridsearch to select the optimal regularization parameter had the best binomial deviance and minimal mean-squared errors (MSE) when $\alpha = 1.0$, equaling a LASSO regression (Hastie and Qian, 2014). For the predictive model with $\alpha = 1.0$, 10-fold cross validation selected the value of λ that minimized MSE ($\lambda = 9.7E\text{-}4$; $\lambda\_1se = 2.4E\text{-}3$). This was the sparsest model, with an accuracy comparable with the best predictive model. The model's AUC was 92% and the obtained coefficients were used as the basis for the gender index. Of the initial 245 potentially sex-related variables (representing 153 unique variables), 92 were excluded from the model and 153 (dummy) variables representing 85 unique variables remained. Many variables were highly indicative of sex. For reasons of clarity all estimated coefficients of nominal and ordinal variables with an OR below 0.5 or above 1.5 and all continuous variables are presented in Appendix C. Most profound were physical activity-related variables (e.g. type of sport activities), work-related variables (e.g. profession), lifestyle (e.g. alcoholic uptake), tasks at home (e.g. cooking and household activities) and personality characteristics. In the model with an AUC of 80% ($\alpha = 1.0$; $\lambda = 0.12$) nine variables remained, related to hours of work, hours of household activities including cooking dinner, and spending leisure time by performing odd jobs (Table 2).

The distribution of the gender index (range: 0–100% feminine) was bimodal. We found median gender indexes of 0.06 (IQR: 0.01, 0.23) for men, and 0.96 (IQR: 0.83, 0.99) for women. In 10.1% (n = 15,480) of the participants the gender index was not in line with their biological sex: 12.5% (n = 7935) of all men scored 50% or higher on the gender index (indicating psychosocial femininity), and 8.4% (n = 7545) of all women scored less than 50% (indicating psychosocial masculinity). Significant interaction terms in two-way ANOVAs showed that the magnitude of the difference in gender index between men and women differed across age groups and educational level, thus analyses were adjusted for age and education.

Table 2
Predictors included in the model correctly classifying 80% of the participants' sex.

Predictor (ordered from strong to less strong)	Odds of being a woman[a]
Always preparing your own dinner	1.30
Days per week light to moderate household activities (0–7)	1.06
Hours per day light to moderate household activities (0–16)	1.06
Hours per week working (0–60 +)	0.99
Days per week of leisure time spend on odd jobs (0–7)	0.99
Hours of leisure time spend on odd jobs (0–12)	0.96
Sometimes preparing your own dinner	0.80
Dinner is always prepared by someone else	0.65
Spending leisure time on odd jobs of light to moderate intensity	0.65

[a] Please note that the odds presented for the continuous predictor variables are per unit change on the scale of the predictor and are thus not directly comparable. ORs below 1.0 are indicative of being a male.

Table 3
The adjusted associations of sex and gender with common somatic symptoms.

Predictor	Sex - female		Gender[a] - feminine	
	OR 95% CI		OR 95% CI	
Outcome				
Headache	1.95	1.88, 2.03	1.34	1.28, 1.40
Dizziness	1.61	1.53, 1.69	1.33	1.25, 1.42
Chest pain	0.92	0.86, 0.99	*1.01*	*0.93, 1.10*
Lower back pain	1.24	1.20, 1.29	1.09	1.04, 1.14
Nausea	1.49	1.42, 1.56	1.24	1.17, 1.32
Painful muscles	1.29	1.24, 1.34	1.07	1.03, 1.12
Difficulties breathing	1.16	1.09, 1.24	*1.02*	*0.94, 1.10*
Feeling hot/cold	3.21	3.05, 3.37	1.24	1.17, 1.31
Numbness or tingling	1.14	1.09, 1.20	1.16	1.09, 1.22
Feeling lump in throat	1.62	1.53, 1.72	1.28	1.20, 1.38
Weakness body parts	*1.03*	*0.99, 1.08*	1.38	1.31, 1.46
Heavy arms or legs	1.27	1.21, 1.33	1.21	1.15, 1.28
	B coefficient 95% CI		**B coefficient 95% CI**	
SCL-90 SOM sumscore	0.09	0.08, 0.10	0.05	0.04, 0.06

NB: The association of sex with common somatic symptoms is adjusted for gender, age and education, whereas the association of gender with common somatic symptoms is adjusted for sex, age and education.

[a] Gender as indicated by the calculated gender index, ranging from 0% (masculine) to 100% (feminine).

We performed our analysis with the gender index that was built upon a population that excluded people with an intersex condition. However, many large cohort studies do not include genetic data in addition to health measures. Thus, participants with intersex conditions in such cohorts cannot be excluded based on a genetic profile. Therefore, we also calculated a gender index based on the complete adult Lifelines population. We found median gender indexes of 0.05 (0.01, 0.22) for men, and 0.97 (0.87, 0.99) for women. A Wilcoxon Signed Rank test for related samples found no statistically significant difference for the gender indexes in both men and women Additionally, the two gender indexes are highly correlated ($\rho > 0.95$).

2.2. Sex and gender, and the association with common somatic symptoms

Sex and gender (i.e. feminine or masculine characteristics) independently associated with common somatic symptoms (Table 3). Significant interaction terms in 9 of the 12 tested symptoms showed that the association of feminine gender characteristics with common somatic symptoms significantly differed per sex for the majority of symptoms. Therefore, we stratified the associations of feminine gender on the common somatic symptoms per sex. Fig. 1 shows that men's experiences of the common somatic symptoms are strongly associated with an increase in feminine gender characteristics. As suggested by all ORs exceeding 1.0, displaying feminine characteristics is associated with a higher common somatic symptom burden of all types. For example, a one hundred-percent increase in femininity score in men, is associated with 1.74 times higher odds on experiencing a one-point increase in severity of dizziness as measured by the SCL-90 SOM. In women, however, feminine characteristics are associated with less chest pain and less difficulties in breathing. The association between feminine characteristics and the sumscore of the SCL-90 SOM was significantly stronger in men than in women. In men, a one hundred-percent increase in feminine characteristics is associated with a 0.09-point increase in the SCL-90 SOM sumscore ($\beta = 0.09$; 95% confidence interval: 0.08,0.10), whereas in women a one hundred-percent increase in feminine characteristics is associated to a 0.02-point increase in the SCL-90 SOM sumscore ($\beta = 0.02$; 95% confidence interval: 0.01,0.03).

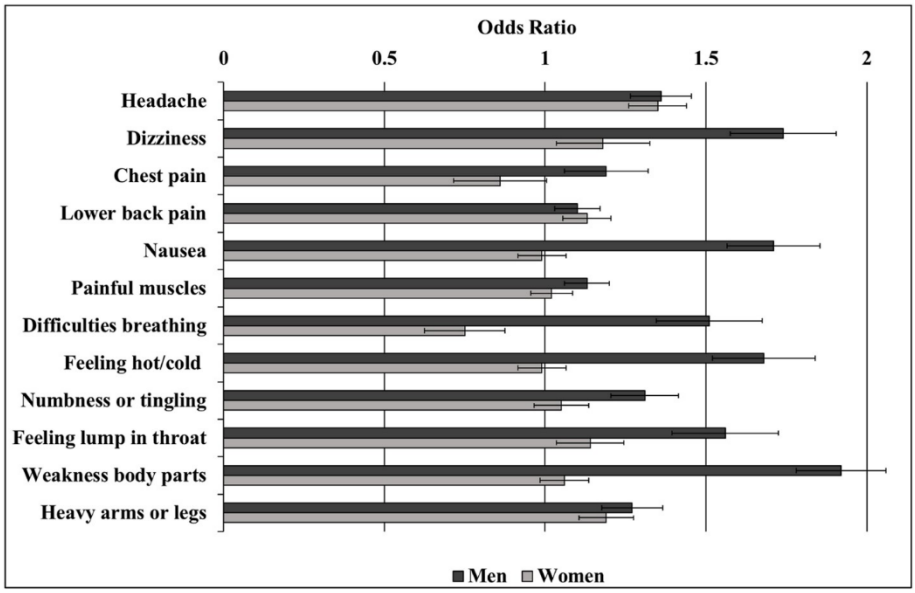

Fig. 1. The associations of feminine gender with reported common somatic symptoms, stratified by sex.

2.3. Sex and gender, and the association with chronic diseases

Table 4 shows that sex and the gender index have an independent association with the lifetime prevalence of most chronic diseases. An increase in gender index, i.e. displaying more feminine characteristics, is associated with an increased risk of chronic diseases. An example hereof is the association between a hundred-percent increase in feminine characteristics and the 1.51-times higher odds on having a stroke. In contrast, female sex appears to be protective of most chronic diseases, except for osteoarthritis, migraine and osteoporosis. Significant interaction terms in five of 12 tested chronic diseases showed that the associations of femininity with lifetime prevalence of chronic diseases significantly differed per sex. Therefore, we stratified the association of femininity with lifetime prevalence of chronic diseases per sex. Fig. 2 shows that in women increases in gender index appeared to be not significantly associated with the lifetime prevalence of chronic diseases, except for migraine (OR = 1.25; 95% confidence interval: 1.16, 1.36). In men, however, increases in feminine characteristics were found to be associated with an increased lifetime prevalence of most chronic diseases.

Table 4
The adjusted associations of sex and gender with the prevalence of chronic disease.

Predictor	Sex – female		Gender[a] – feminine	
	OR	95% CI	OR	95% CI
Outcome				
CVD	0.88	0.82, 0.91	1.17	1.09, 1.26
Epilepsy	0.66	0.57, 0.78	1.60	1.34, 1.91
Asthma/COPD	*1.01*	*0.95, 1.06*	1.08	1.02, 1.15
DM1	0.54	0.37, 0.79	*1.44*	*0.91, 2.27*
DM2	0.48	0.42, 0.55	1.91	1.61, 2.26
Stroke	0.57	0.46, 0.71	1.51	1.16, 1.97
Osteoarthritis	1.68	1.55, 1.82	*1.09*	*0.98, 1.20*
Skincancer	*1.16*	*0.99, 1.35*	*1.13*	*0.96, 1.34*
Kidney failure	*1.08*	*0.95, 1.22*	1.19	1.02, 1.38
Migraine	2.37	2.25, 2.49	1.27	1.19, 1.35
Osteoporosis	4.73	3.89, 5.75	*1.07*	*0.86, 1.33*
Rheumatoid arthritis	*1.04*	*0.91, 1.19*	1.55	1.32, 1.83

NB: The linearity assumption for logistic regression between gender and CVD, skin cancer, epilepsy and asthma/COPD was violated. Therefore, results here are the odds of the highest gender quartile compared to the lowest gender quartile. The associations of sex with the prevalence of chronic diseases is adjusted for gender, age and education, whereas the association of gender with the prevalence of chronic disease is adjusted for sex, age and education.

[a] Gender as indicated by the calculated gender index, ranging from 0% (masculine) to 100% (feminine).

2.4. Sensitivity analyses

To explore the possibility that the associations were identified due to respondents' health status, rather than gender roles, a sensitivity analysis was performed by excluding physical activity-related predictors. The analysis showed that composition of the gender index remained similar, and was highly correlated to the original gender index ($\rho > 0.95$) as well. In addition, the associations of the gender index without physical activity-related variables with common somatic symptoms and chronic diseases remained similar to those found with the original gender index. To explore the influence of the imputations, we performed a second sensitivity analysis based on respondents with complete data. The analyses showed that again that the composition of the gender index remained mostly comparable and was highly correlated to the original gender index ($\rho = 0.95$). Additionally, the associations of the gender index with common somatic symptoms and chronic diseases remained comparable. Results of both sensitivity analyses are provided in the electronic supplementary materials.

3. Discussion

We found that a higher gender index (i.e. tending towards feminine characteristics) and sex are independently associated with common somatic symptoms and lifetime prevalence of chronic diseases. Feminine characteristics are associated with experiencing a higher common somatic symptom burden and chronic diseases, especially in men. Female sex is also associated with a higher burden of common somatic symptoms, but not to all chronic diseases, compared to male sex. In 10.1% of the participants, the gender index was not in line with participants' sex, as in 12.5% of men and 8.4% of women a discrepancy between gender index and sex was found.

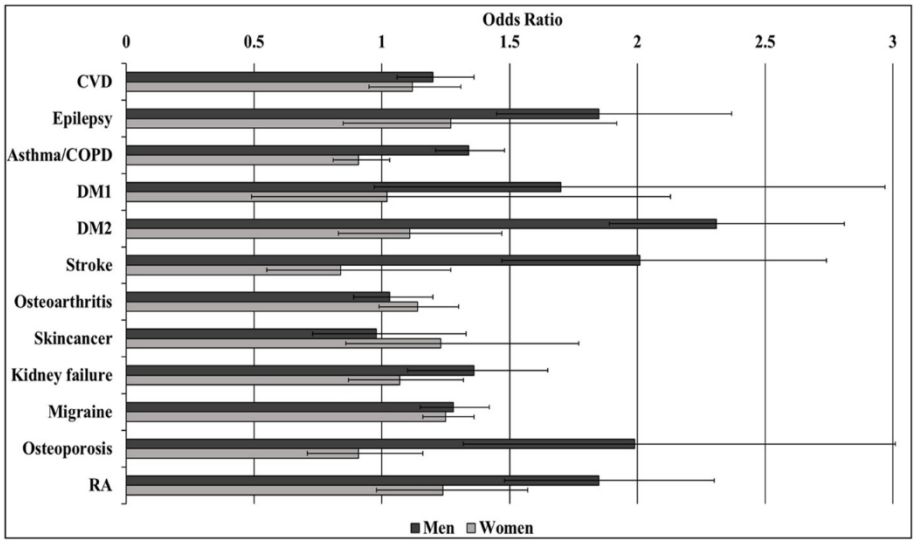

Fig. 2. The associations of feminine gender with reporting chronic diseases, stratified by sex.

3.1. Strengths and limitations

This study has some strengths. First, LifeLines includes a large sample size in which many psychosocial variables were assessed. This allowed us to incorporate a wide range of gender-related psychosocial candidate variables into the model. Furthermore, it assured strong statistical power. Second, the current method of calculating a gender index follows a data-driven approach, whereas most previously established gender indexes follow a theory-driven approach (Bem, 1974; Lippa and Connelly, 1990; Pelletier et al., 2015; Smith and Koehoorn, 2013). Both approaches have their respective advantages and disadvantages. A data-driven approach allows for a model to include a wide range of psychosocial characteristics to construct a gender index and to move beyond merely operationalizing gender roles by means of personality characteristics. Furthermore, it allows to establish a time- and place-dependent gender index since the index is constructed based on psychosocial differences between biological sexes in the cohort under study. In other words, the method is flexible and adaptive and can be applied to calculate a gender index specific to the study's context. Other studies do not necessarily need to rely on genetic data of participants to exclude people with indeterminate binary sex, as we showed that excluding the people with an intersex condition from a large general population cohort did not change the constructed gender index significantly. However, one should note that the estimated coefficients are chosen merely based on maximizing predictive accuracy of a model and the nature of the predictors is ignored. That is, when two variables are equally contributing to improving the model's predictive accuracy, the algorithm randomly chooses one of the predictors. Additionally, the gender index proposed here is a study-specific measure for gender roles that cannot be generalized to other studies: although the method is applicable in other studies, the exact construct of the gender index will vary across settings.

A theory-driven gender index allows for easier comparison across studies and its interpretation is more straightforward than that of a data-driven gender index. However, it should be noted that a theory-driven gender index cannot handle the time- and place-dependent nature of (the embodiment of) gender roles, i.e. the relevance of the index might differ between studies performed at different times or at different places. Given these advantages and disadvantages of both approaches, a combination of a theory-driven approach (in which potential gender-related variables are selected based on theory or expert opinion) and a data-driven approach (in which an algorithm maximizes the predictive accuracy of the model underlying the gender index) may yield the easiest interpretable and most trustworthy gender index.

Limitations of the study should be acknowledged as well. First, we did not include a gold standard gender measure, as this does not exist yet (Schiebinger and Stefanick, 2016). Thus, our gender index was not validated with other measures. Second, this study is not gender-expansive, as it does not move beyond the male/female binary. Therefore, our results are not directly applicable to agender or non-binary people. Third, lifetime prevalence of chronic diseases was self-reported, which could cause response and recall bias. These biases might differ between women and men. Several studies suggest that men are less willing to report health problems and report health problems at a later time than women (Singh-Manoux et al., 2008; Hausteiner-Wiehle et al., 2011), Therefore, the reported association of female sex -and by inference that of femininity-with chronic diseases might be an overestimation. Last, this study had a cross-sectional design, which does not allow for any causal inference of the effect of gender on common somatic symptoms or chronic diseases, or vice versa. Therefore, no causality can be concluded from the study. In addition, we cannot exclude the possibility that the reported associations are partly spurious, since the predictors on which the gender index is based may not only reflect respondents' gender roles but also their general health. However, a sensitivity analyses using a gender index that was estimated without physical activity-related variables showed that the associations of sex and gender with health outcomes remained comparable, suggesting that the reported associations are largely meaningful.

3.2. Sex and gender, and the relation to common somatic symptoms and chronic disease

To the authors' knowledge, this is the first study in which gender indexes were derived in a data-driven manner, i.e. without pre-specified variables. The defined model displayed 92% accuracy in distinguishing between sexes, indicating that the included psychosocial variables are

strongly connected to being a man or a woman in the LifeLines Cohort. . The variables with the highest predictive value for sex (i.e. work-related and household-related variables, and dedicating leisure time to odd jobs) in the current study, were in concordance with previous studies (Lippa and Connelly, 1990; Pelletier et al., 2015; Smith and Koehoorn, 2013). A newly identified variable within the realm of household-related variables that strongly discriminates between sexes included the frequency in which one prepares his or her own dinner.

We found that household-related activities had strong predictive value in discriminating between sexes. A Swedish study found 2.2-fold higher odds on experiencing common somatic symptoms for women who had many domestic duties, compared to women with few domestic duties (Krantz and Ostergren, 2001). Follow-up studies replicated this: women with jobstrain and domestic duties had higher odds on experiencing common somatic symptoms than women with jobstrain and no domestic duties (Krantz et al., 2005; Mellner et al., 2006). These studies support the idea that female gender roles are more stressful and less gratifying than male gender roles, which might lead to worse health outcomes (Nathanson, 1975). Household responsibilities have been associated with lower access to health care in both men and women (Pelletier et al., 2014), suggesting that healthcare factors might explain health-related gender differences as well. Finally, we cannot exclude reverse causality, in which experiencing common somatic symptoms results in less paid working hours and therefore conducting more household-related activities (van der Leeuw et al., 2015).

Literature on the association of gender with common somatic symptoms and chronic diseases is scarce. Although many studies do not explicitly distinguish between sex and gender in health (Regitz-Zagrosek, 2012; Hankivsky et al., 2018), some studies suggest that differences in gender roles are mediating sex differences in experienced health (Robinson et al., 2001; Alabas et al., 2012; Pelletier et al., 2016). The current study also shows that female sex and feminine gender roles are independently associated with increased common somatic symptoms. Earlier research has shown that female sex is a risk factor for a variety of symptoms (Barsky et al., 2001; Tomenson et al., 2013). Our findings show that female sex compared to male sex is associated with an increased lifetime prevalence of osteoporosis, migraine and osteoarthritis, which is in line with previous studies (Hame and Alexander, 2013; Alswat, 2017; Schroeder et al., 2018). The current results also suggest that male sex was associated with an increased prevalence of CVD, which is in line with the traditional, yet increasingly defeated, idea of CVD being '*a man's disease*' (Wenger, 2012; Humphries et al., 2017). However, it must be noted that underdiagnoses of -amongst others-cardiovascular diseases, still tends to occur in women, despite improvements made over the last decade (Wenger, 2012). Additionally, women might undergo different (diagnostic) care trajectories than men, rendering women with more delayed or wrong diagnoses (Arber et al., 2004, 2006). This underreporting might partly explain the protective association of female sex with cardiovascular disease.

To the authors' knowledge, this is the first study to show that feminine gender is associated with an increased burden of common somatic symptoms and a higher lifetime prevalence of chronic diseases, especially in men. This is in line with previous studies that showed that higher frequencies of common somatic symptoms are reported in gender dysphoric (i.e. people in whom sex assigned at birth and current gender identity do not match) and gender non-conforming individuals, than in cisgender individuals (Heylens et al., 2014; Colizzi et al., 2015; Serpe, 2017; Shirdel-Havar et al., 2019). More specifically, significantly higher SCL-90 SOM scores were reported in male-to-female transsexual and transgender individuals than in cisgender men (Auer et al., 2013). These increased rates of common somatic symptoms are often attributed to the psychological distress that is inherent to gender dysphoria. The inability to adhere to imposed societal norms on masculinity and femininity is theorized to cause anticipated and internalized stigma in these individuals, which results in a higher chance of reporting somatic symptoms (Serpe, 2017). Although the feminine men in our study are not necessarily gender dysphoric (they merely display more feminine than masculine characteristics) the psychological distress that accompanies the non-adherence to societal norms on gender roles together with the stress that accompanies female gender roles could have affected these participants as well. Only one previous study amongst the general population tested whether femininity was associated with common somatic symptoms. This study found no significant association, but had a relatively small sample size and used the BSRI (Castro et al., 2012). No distinction between sexes was made in this study.

In conclusion, incorporating one's gender roles and sex in care trajectories could aid the process of effective medicine, tailored to the societal circumstances in which gender roles are shaped. Therefore, we recommend to conduct further research to explore the effect of gender on health outcomes in clinical settings. In line with this, research could focus on the association of gender with established risk factors for disease, instead of the disease itself, for this might allow for more effective preventative interventions. Additionally, a longitudinal study design could be useful to explore possible reverse causality between gender roles and health and to obtain insight into the relation between the two concepts. We also suggest to set a stricter distinction between gender and biological sex in research and literature, as these concepts are often applied interchangeably. Lastly, we recommend the consideration of gender in large cohort studies, as our methodology shows this is feasible.

CRediT authorship contribution statement

Aranka V. Ballering: Formal analysis, Methodology, Visualization, Writing - original draft, Writing - review & editing. **Irma J. Bonvanie:** Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **Tim C. Olde Hartman:** Conceptualization, Writing - original draft, Writing - review & editing. **Rei Monden:** Methodology, Writing - original draft, Writing - review & editing. **Judith G.M. Rosmalen:** Conceptualization, Project administration, Supervision, Writing - original draft, Writing - review & editing.

Declaration of competing interest

None.

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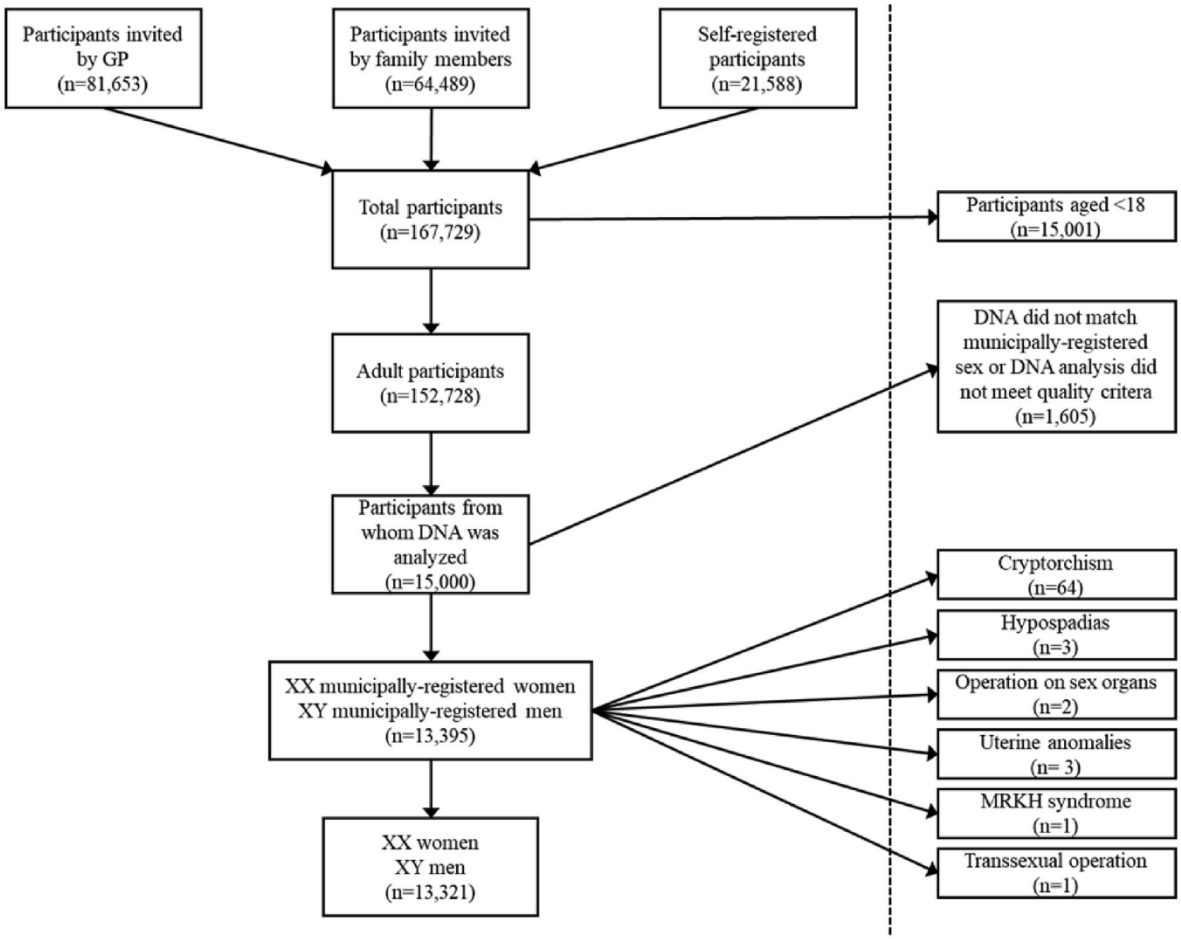
Appendix A

A.1 Potential Intersex Conditions

Copy number variations of the sex chromosomes			
45, X0	46, XX/XY	47, XXY	47, XXX
48, XXXX	48, XXYY	49, XXXXX	49, XXXXY
Genetic mutations			
5α-reductase deficiency		Congenital adrenal hyperplasia	
17β-Hydroxysteroid dehydrogenase deficiency		Androgen insensitivity syndrome	
Aromatase deficiency		Aromatase excess syndrome	
Isolated 17,20-lyase deficiency		Leydig cell hypoplasia	
Lipoid congenital adrenal hyperplasia		Swyer Syndrome/Gonadal dysgenesis	
Developmental variations of internal and/or external sex organs			
Aphallia		Diphallia	
Micropenis		Cryptorchism	
Müllerian agenesis (MRKH syndrome)		Clitoromegaly	
Pseudovaginal perineoscrotal hypospadias		Uterus didelphys	
Uterus unicornis		Additional uterine anomalies	
Aposthia		Hypospadias	

A.2 Sampling method



A.3 Number of participants with potential intersex and/or non-conform gender identity, within the complete Lifelines sample and the subsample from whom DNA passed quality control

Type of potential intersex condition and/or indication of transgender identity	Adult Lifelines Cohort (n = 152,728)	Subsample (n = 13,395)
Copy number variations of sex chromosomes		
Turner	11	0
Klinefelter	13	0
Genetic mutations (hormonal/metabolic)		
Congenital adrenal hyperplasia	8	0
Congenital variations of internal and/or external sex organs		
Hypospadia	53	3
Cryptorchism[a]	1106	64
Operated for dysplastic or divergent sex organs[b]	42	2
Primary hypogonadism	10	0
Ovarian tube(s) missing or underdeveloped	7	0
Uterine anomalies	28	3
Müllerian agenesis (MRKH syndrome)	11	1
Gonadal dysgenesis (Swyer syndrome)	1	0
Non-conform gender identity		
Expressed gender dysphoria or non-conform gender identity and/or transgender medication use and/or transsexual operation(s)	19	1[c]
Total	1309 (0.86%)	74 (0.55%)

[a] Cryptorchism included if present at adult age and/or reported as operated:99% of the 1106 participants who reported cryptorchism, reported it as operated.
[b] e.g. “no vagina”, “vaginal septum”, “divergent sex organs adjusted”.
[c] The participant informed the researchers of the change in sex in the municipal registration and was thus not excluded during the quality control procedures of the genetic material.

Appendix B. –Categories of variables included in LASSO regression

Categories	
1	General information and demographics
2	Current and past relationships
3	Living situation
4	Education and work
5	Social activities and wellbeing
6	Lifestyle
7	Diet and weight beliefs
8	Threatening experiences and long-term difficulties
9	Personality (NEO-PI-R)

Note: Detailed information on the included variables are included as electronic supplementary material.

Appendix C. Nominal and ordinal predictors (odds > 1.5 or < 0.5) and all continuous predictors in the model with 92% predictive ability of the participants' sex

Nominal and ordinal predictors (ordered from strong to less strong)	Odds of being a woman
Performing sport activity: horseriding	6.89
Performing sport activity: zumba[a]	5.58
Performing sport activity: soccer	0.19
Profession: crafts and related trades workers	0.21
Always preparing your own dinner	4.34
Being retired	0.26
Drinking alcohol 6–7 days a week	0.27
Doing leisure time odd jobs of moderate intensity	0.28
Dinner is always prepared by someone else	0.32
Drinking alcohol 3 days a week	0.32
Profession: plant and machine operators and assemblers	0.32
Currently in a job	2.99
Being a housewife or househusband	2.82
Short period of time dieting	2.56
Drinking alcohol 4–5 days a week	0.40
Doing leisure time odd jobs of light intensity	0.41
Drinking alcohol 1 day a week	0.42
Profession: skilled agricultural, forestry or fishery workers	0.44
Performing sport activity: gymnastics	2.26
Often preparing your own dinner	2.15
Losing one's job and not able to find new work	1.99
Profession: services and sales workers	1.77

Unpleasant experience: got in trouble with the law or police in the past year	1.73
Profession: clerical support workers	1.55
Performing sport activity: swimming	1.54
Experienced difficulties and stress in the relationship with ones parents	1.53
Continuous predictors (odds per unit change on respective scale)	
Higher mean scores on the self-discipline scale of the NEO (range: 0–4)[b]	1.52
Higher mean scores on the impulsiveness scale of the NEO (range: 0–4)[b]	1.38
Higher mean scores on the self-consciousness scale of the NEO (range: 0–4)[b]	1.38
Number of household members smoking (range: 0–6 +)	1.29
Hours per day light to moderate household activities (range: 0–16)	1.29
Higher mean scores on the vulnerability scale of the NEO (range: 0–4)[b]	1.29
Hours per day vigorous household activities (range: 0–16)	1.25
Hours sleep per 24 h (range: 4–20)	1.19
Days per week light to moderate household activities (range: 0–7)	1.13
Higher scores on the competence scale of the NEO (range: 0–4)[b]	1.08
Days per week light to moderate household activities (range: 0–7)	1.04
Number of times moved house (range: 0–25 +)	1.01
Percent declared unfit for work (range: 0–100%)	0.99
Days per week walking (range: 0–7)	0.98
Days per week at least 30 min light to moderate work (range: 0–7)	0.97
Number of cigars smoked per day (range: 0–10 +)	0.97
Hours per day light to moderate work (range: 0–16)	0.96
Hours per week volunteering (range: 0–60)	0.95
Hours per week working (range: 0–60)	0.94
Number of co-residents (range: 0–6 +)	0.93
Hours per day TV-watching (range: 0–8)	0.92
Hours per day cycling (0–12)	0.90
Higher mean scores on the deliberation scale of the NEO (range: 0–4)[b]	0.88
Hours per day odd jobs (range: 0–12)	0.86
Days of the week odd jobs (range: 0–7)	0.85
Higher mean scores on the hostility scale of the NEO (range: 0–4)[b]	0.80
Higher mean scores on the excitement scale of the NEO (range: 0–4)[b]	0.51

NB: An OR below 1.0 indicates being a man.
[a] Zumba is dance-based type of fitness.
[b] Mean subscale scores of the NEO-PI-R.

Appendix D. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.socscimed.2020.112968.

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